develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* The Wyeth Laboratories' submission includes an excellent summary description of the preparation of the two toxoids. The final product is a combined antigen product, including in each 0.5 mL dose, 5 Lf of tetanus toxoid, 1.38 Lf of diphtheria toxoid, and 0.34 mg of aluminum as aluminum phosphate. Sodium chloride is added to the final product as necessary to establish isotonicity.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary and booster immunization of children over the age of 6 and adults against diphtheria and tetanus. The recommended number of doses and intervals between doses are consistent with recommendations of the Public Health Service Advisory Committee on Immunization Practices. The package insert emphasizes that this product should not be used for basic immunization or booster dosing in infants and children under 6 years of age.

b. *Contraindications.* Acute active infections are listed as a relative contraindication, except in the event that emergency booster dosing is required. An outbreak of poliomyelitis is said to be reason to defer elective immunization.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A recent report by McCloskey (Ref. 5) provides satisfactory evidence of the efficacy of Wyeth Laboratories' diphtheria and tetanus toxoids, adsorbed (for adult use), when used as a booster dose. He boosted 123 adult hospital workers with Td toxoid, containing 1 Lf of diphtheria toxoid, and found no diphtheria antibody response in 21 percent of this group 1 month later. Their preimmunization titers for diphtheria antibody were less than 0.01 unit per mL, and all of those who failed to respond had either never been immunized against diphtheria or had been immunized more than 10 years prior to inclusion in this study. This data provided reasonable evidence of satisfactory human immunogenicity for the diphtheria component when used as a booster dose. No data were provided for the efficacy of this product when used in primary immunization.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Adequate evidence is presented in the report of Sisk and Lewis (Ref. 6) of the safety of Td toxoid, as prepared by Wyeth Laboratories, when used as a booster dose. No evidence of safety is provided for the use of this product in primary immunization.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization cannot be assessed with certainty, owing to the absence of acceptable data regarding its efficacy. The benefit-to-risk assessment for this product when used for booster immunization is satisfactory.

4. *Critique.* The labeling is generally satisfactory. The labeling is well written, the recommendations for use are consistent with advisory bodies such as the Public Health Service Advisory Committee on Immunization Practices, and the indications for use of this product are clearly delineated. It is probably unnecessary to continue to refer to outbreaks of poliomyelitis as reasons for deferral of elective immunization.

The major defect in the submission is the lack of human data on the safety and immunogenicity of this product when used as a primary immunizing agent.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards the use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop evidence regarding the efficacy of this product when used for primary immunization.

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Generic Statement

Pertussis Vaccine

Pertussis, or whooping cough, is a bacterial infection caused by *Bordetella pertussis* (formerly *Haemophilus pertussis*) and is characterized by severe and paroxysmal coughing which persists for some weeks. The disease affects primarily infants and young children, and its morbidity and mortality rates are inversely related to age. Infants do not acquire adequate immunity from their mothers and are therefore highly susceptible to infection. The infection is localized in the respiratory tract, especially on the epithelial surfaces of the bronchial tree. The paroxysms of coughing ("whoop") are believed to be caused either by the tenacious nature of the secretions or conceivably by an effect of the disease process on the nervous system. Immediate complications include encephalopathy and convulsions, pulmonary atelectasis, and secondary infections such as pneumonia and otitis media. Developmental retardation and bronchiectasis may occur as permanent sequelae.

Pertussis responds poorly to treatment with antimicrobial drugs. Erythromycin and ampicillin, the two most commonly used antibiotics, are effective only if given in the earliest stages, although secondary complications caused by bacteria other than *Bordetella pertussis* usually respond satisfactorily.

In the United States, morbidity and mortality due to pertussis rapidly declined after increased utilization of pertussis vaccine in the 1940's and its official standardization in 1949, although the disease persists as a significant contributor to infant mortality in developing countries. Indeed, the crude mortality rate from pertussis in this country decreased by 1967 to one two-hundred fiftieth of the 1930 rate; in 1973 only five deaths due to pertussis were reported. However, not all of this remarkable decline can be attributed to widespread use of the vaccine, for the reason that some decline in morbidity and morality from pertussis was observed in the United States and other Western countries, prior to the institution of immunization. Nonetheless, the inference that part of the decrease is due to the vaccine is supported by an increase of pertussis in England where vaccine of low potency had been used. In addition, the disease has increased in countries, including Denmark, England, and Japan, where the use of vaccine was decreased because of the fear of severe reaction.

Despite these favorable mortality trends, pertussis is far from eradicated in the United States. The disease is ubiquitous although its incidence is low. The exact rates, however, are unknown for several reasons. Cases are frequently

unreported or not recognized. Since verification of infection by isolation of the organism requires cultural methods not routinely used in many diagnostic laboratories, the infection may go undiagnosed. Further, serologic testing is not feasible for routine diagnosis. Infection in immunized persons may cause bronchitis but without typical whooping. Therefore, reports of pertussis obtained by the Center for Disease Control probably represent only a fraction of all pertussis infections occurring in the country.

The results of early studies of pertussis vaccines in the 1920's were encouraging, but far from satisfactory. Subsequent technical improvements in vaccine production included the use of freshly isolated and more immunogenic strains for vaccine production and later the testing of the potency of the vaccine by intracerebral challenge of vaccinated mice, a test that appears to correlate satisfactorily with the immunogenicity of the whole bacterial vaccine in children. Further, agglutination titers in the blood of vaccinated humans were found to correlate reasonably well with protection against disease. However, it should be noted that immunity achieved in man following the natural disease or immunization is not always absolute or permanent. Pertussis occasionally occurs in older children and adults with a history of prior immunization or infection.

Careful evaluation of several vaccines was conducted in Great Britain by the British Medical Research Council in the late 1940's and 1950's. Efficacy was estimated from home exposure rates, and the results showed that the most effective vaccines protected 90 percent or more of children from clinical disease. Vaccines lower in mouse potency were less effective. Other studies have also correlated the laboratory-assayed potency with clinical efficacy.

Description

Current pertussis vaccine are aqueous preparations of either killed whole *Bordetella pertussis* bacteria of a fraction of *Bordetella pertussis* bacteria. The vaccines may be fluid or adsorbed, and may be combined with other antigens.

In contrast to some other immunizing agents, such as diphtheria and tetanus toxoids, pertussis vaccine is a relatively crude preparation that contains the majority of the bacterial constituents, most of which are probably not relevant to the induction of immunity to the disease. The reason for this vaccine being impure is that the antigenic component of the bacterium responsible for clinical immunity has not yet been positively identified. There is one combined product presently licensed (a modified DTP) that contains a partially fractionated pertussis component and the relative efficacy of this product, compared to the whole bacterial pertussis vaccine, has not been determined in controlled field trials.

Production

Pertussis vaccine is made from cultures of one or more strains of phase I *Bordetella pertussis* that yield the required potency. The composition of the culture media must meet Federal regulations.

The bacteria are killed and detoxified by heating, addition of a chemical agent, and appropriate aging, or an acceptable combination of these. The bacterial content must meet requirements specified in terms of the U.S. Opacity Standard. Vaccine potency is determined by comparing the results of the mouse protection test with that of the U.S. standard pertussis vaccine. A preservative, usually thimerosal, is added.

Federal regulations require that each lot of pertussis vaccine be tested in mice for immunogenicity prior to release. In this test, mice immunized with the vaccine lot are challenged intracerebrally with live organisms, and the results compared with those in mice similarly immunized with the U.S. Standard Pertussis Vaccine. The essential procedures for the test and its interpretation are specified in the Code of Federal Regulations (21 CFR Part 620).

The test provides a means of estimating the mouse potency of the vaccine lot. It must have a mouse potency of 12 protective units per total human immunizing dose (3 doses), except that for the vaccine in the combined product containing poliomyelitis vaccine the potency may be no less than 14 units.

Use and Contraindications

Currently, in the United States it is recommended that routine immunization begin at 2 or 3 months of age. Although monovalent pertussis vaccine is available, the trivalent product, with tetanus and diphtheria toxoids (DTP), is preferable. Earlier immunization may be undertaken if the disease is unusually prevalent in the community, but the immune response of very young infants is less satisfactory than that of older infants. The usual primary immunization schedule comprises the intramuscular administration of DTP on four occasions: 3 doses containing 4 protective units of pertussis vaccine each at 4- to 8-week intervals with a fourth dose approximately 1 year after the third injection. A booster dose, preferably at the time of school entrance, is recommended. Administration of pertussis vaccine is generally not recommended after the age of 6 years because of the possibility of increased rates of adverse reactions and the fact that the disease is less severe in those 6 years or older, and because it has not usually appeared necessary for continuing protection. Rarely, in the presence of a community outbreak of pertussis, a booster dose of pertussis vaccine has been administered to older children and adults at risk, sometimes as a half dose (2 protective units).

An acute febrile illness is usually reason to defer immunization in order to avoid confusion as to the cause of subsequent fever and because of the possibility of an additive effect. The occurrence of an apparent severe reaction to the administration of any preparation containing pertussis vaccine requires consideration of modifying the subsequent dosage schedule. Significant reactions that have been attributed to pertussis vaccine have included high fever (greater than 39.5° C), a transient shock-like episode, excessive screaming, somnolence, convulsions, encephalopathy, and, extremely rarely, thrombocytopenia. Such reactions almost always appear within 24 to 48 hours after injection, but have been thought to occur after an interval as long as 7 days. Shock, convulsions, encephalopathy, excessive screaming, and thrombocytopenia, if believed by the physician to be due to the pertussis antigen, represent absolute contraindications to further administration of this vaccine. In the case of young children receiving combined preparations, immunization with the components of the preparation other than pertussis should be continued, usually as diphtheria and tetanus toxoids combined (DT). High fever and somnolence do not represent absolute contraindications to continuing immunization against pertussis, but the physician should exert caution and may wish to consider fractional doses for subsequent injections.

Safety

Federal regulations require manufacturers to test each lot of vaccine for toxicity in mice prior to release. In this test, evidence of toxicity comprises failure of mice to achieve specified weight gain when injected intraperitoneally with one-half the single human dose. Different strains of mice may vary in their rates of weight

gain and specifications for suitable test strains may be necessary. In addition to the toxicity test, each lot of vaccine must under go a general safety test using animals and a sterility test. These tests are described in Title 21, Part 600, Code of Federal Regulations. In addition, it is expected that manufacturers keep records of all reactions in humans reported to them, and that these records be available to the Bureau of Biologics on request.

In spite of these precautions, untoward reactions to pertussis vaccine in humans occur. Low-grade fever and local tenderness appear frequently after injection. The severe of disturbing untoward reactions, including shock, convulsions, encephalopathy, persistent high-pitched screaming, and thrombocytopenia, are rare complications, the rates of which are difficult to define precisely, at least in part because they are often not reported. However, as morbidity and mortality from pertsussis have declined, these reactions have drawn considerable attention. The frequency of fatal reactions has been estimated to be 1 or 2 cases per 10 million injections in the United States. As with the neurologic complications of the disease, the mechanism of the untoward reaction is not understood. A responsible component in pertussis vaccine has not been identified, nor has any characteristic of vaccine recipients that predisposses to such reactions been found, although some observers have suggested that children with a history of convulsions are at higher risk. Observations in this and other countries indicate that vaccine, of excessively high potency may be more reactive.

Pertussis vaccine adsorbed onto aluminum compounds elicit fewer adverse reactions and are thought to provide better and longer protection. The adsorbed vaccines are comparable to plain vaccines in the mouse weight-gain test and are approximately twice as immunogenic per bacterial content in the mouse potency assay. Pertussis vaccines potentiate the antitoxin response to diphtheria and tetanus toxoids, and thus it is advantageous to provide primary immunization to infants with a combination of pertussis vaccine and these toxoids (see Generic Discussion of DTP).

Efficacy

Studies reported by the British Medical Research Council in the 1950's showed good correlation of the mouse protection test results with clinical protection. Based on these results and those of other studies, the mouse potency test has been accepted as an indication of efficacy in lieu of field studies. In addition to the mouse protection test, agglutination titers in the sera of those vaccinated in the British studies were found to correlate fairly well with efficacy. Agglutination titers of 1:320 or better were associated with protection in field studies. One notable exception was observed with a partially purified soluble antigen. This vaccine was found to be highly efficacious in terms of clinical protection but did not cause an aggultinin response except to the specific serologic strain that was used in the soluble antigen production. In other instances, it was observed that protection may sometimes exist in the presence of low agglutinin titers, but in general the presence of agglutinins seems to reflect immunity, though indirectly. Therefore, the agglutination test may be used to evaluate vaccine potency when the incidence of the disease is too low for meaningful field studies of clinical protection, a situation that exists in the United States at the present time.

Later in the 1960's low efficacy of British vaccines was reported. Subsequent analysis attributed these failures to use of a standard vaccine that contained 2 instead of 4 protective units per single dose.

Protection from disease is directly related to interval since vaccination. The extent to which vaccination modifies the disease, rather than prevents infection, is unknown.

Although the immunogenicity of pertussis vaccine is less, and the reactivity higher than most other commonly used vaccines, all evidence supports the belief that the benefits of universal pertussis immunization considerably outweigh the adverse effects. The morbidity, mortality, and neurological complications of immunizations are significantly less than those of the disease.

Special Problems

Although clearly of great value, pertussis vaccines do not exhibit the effectiveness and safety that have been achieved with certain other immunizing agents. Specific problems that deserve investigative pursuit may be grouped in three categories.

1. The pathogenesis of the disease and the biology of the organism are poorly understood. As a consequence, knowledge of the immune response and the mechanisms of complications of both the disease and immunization is limited.

It is not known what components of the organism are responsible for the clinical and pathologic features of the disease and its complications, or how they act. It is not known what component of the organism produces immunity, whether it is a single antigen, if it relates to the components that produce the disease characteristics, or whether it is identical to the mouse-protective antigen. Further, the biologic attributes of the organism that produce the neurologic complications of the disease have not been identified, nor is it clear that they are the same as those responsible for the neurologic sequelae of immunization.

Current pertussis vaccines are complex mixtures of reactive cellular substances. Some progress toward identification of the mouse-protective antigen has been made over the past 10 years. This component appears to be associated with the fimbriae and parts of the cell envelope. Whether the histamine-sensitizing and the lymphocytosis-promoting factors can be separated from the protective antigen is unclear.

Until better definition of the components of the organism and their relation to disease and immunity are established, the effect of attempts to improve immunogenicity and reduce reactivity of pertussis vaccines by purification or extraction can only be evaluated by costly and logistically difficult field studies in humans.

2. The current epidemiology of pertussis and that of vaccine-induced complications are not defined with satisfactory precision.

As noted previously, reported cases of pertussis probably represent only a fraction of those occurring. Without adequate surveillance of disease rates, the effectiveness of current vaccines and immunization programs cannot be monitored.

Although there is evidence of worldwide shifts in the major antigenic characteristics of pertussis strains causing clinical disease, it is not known whether these shifts have diminished the effectiveness of pertussis vaccine. Changes in the distribution of serotype antigens in disease isolates from populations undergoing immunization have been demonstrated in several different geographic areas. These shifts in serotypes have prompted changes in pertussis strains used for vaccines in certain countries. However, experimental evidence indicates the serotypes are not necessarily protective moieties and the vaccine potency has not been related to these bacterial antigens. Studies that suggest an increase in pertussis in immunized children because of shifts in the wild organism cannot be interpreted because the protective unitage of the vaccines

was not taken into account. However, there is no firm evidence, as of now, that it is important to modify pertussis vaccines so that the immunizing strains reflect the strains prevalent in the community. This problem cannot be evaluated without better surveillance.

Experience with modern pertussis immunization is not of sufficient duration to predict whether childhood immunization may in some instances postpone natural infection until a later age. The disease itself does not always assure life-long immunity. Further, it is possible that in the past, when the disease was more widespread, periodic exposure to pertussis provided reinforcement of immunity throughout life; if such naturally occurring boosters did contribute to the protection of older children and adults, low prevalence of the disease in recent years may be reflected by the appearance of a susceptible older population. Thus, the possible need to immunize adults, as well as children, may have to be considered in the future. This will require weighing the risks of widespread immunization of older children and adults against the fact that the disease in these age groups is milder than in young infants. Current data related to this question are inadequate for rational decisionmaking.

On the other hand, the usefulness of the currently recommended booster dose at school entrance has never been fully documented. Presumably, by keeping school children free from pertussis, transmission to younger siblings in the home is prevented. Whether this final booster offers additional protection from disease and/or such transmission is unproved.

The rates of severe untoward reactions to pertussis vaccines are not defined. Furthermore, the ultimate significance, if any, in terms of permanent sequelae, of vaccine-induced somnolence, excessive screaming, and high fever is unknown, and without such knowledge satisfactory recommendations for further immunization cannot be made if any of these reactions occurs. Physicians are expected to report complications of immunization to manufacturers in the United States, but compliance with this expectation is less than optimum. Many physicians are not cognizant of the importance of reporting untoward reactions or may be unaware of their clinical features. Further, both physicians and manufacturers may be held liable for damages in suits brought by patients who may suffer adverse effects from established vaccines. All these factors undoubtedly discourage reporting; without maximum reporting or some other form of surveillance, definition of the rates and significance of untoward reactions to current and future vaccines cannot be ascertained.

3. Laboratory procedures and technical requirements for the production and evaluation of pertussis vaccine exhibit certain problems that require solution.

The results of the weight-gain test in mice, used to determine toxicity of the pertussis vaccine, show variability between laboratories and therefore either the test requires more precise standardization or another method for determining toxicity is needed. This is a problem for both the test vaccine and the control reference vaccine. At present the only test shown to have any relation to clinical reactivity in man is the mouse weight-gain test.

Section 620.4(g) (21 CFR 620.4(g)) states that pertussis vaccine shall have a potency of "12 units per total human immunizing dose." Certain statistical variations in estimates of actual potency that provide some assurance that the product probably does contain 12 units per total human immunizing dose are permitted based on the number of assays performed. This is in recognition of inherent variability in this type of assay. Identification and improved control of the factors influencing the variability of this test is needed.

Further, definition of the total immunizing dose in the regulations as 12 units (3 doses of 4 units each) is now at variance with current practice and the recommendations of national advisory committees in that 4 doses of 4 units each are now advised and employed (see section on Use and Contraindications).

During the first studies of efficacy, agglutination tests were carried out by tube dilution, which required rather large amounts of sera. The microtests in general use today need to be standardized, since there is a tendency for each laboratory to use its own adaptation of the test, making comparisons among results from different laboratories almost impossible. However, agglutination antibodies may only be indirectly associated with protection, and may not constitute the protection-specific antibody. A more specific test should be substituted if and when it becomes available.

Recommendations

1. The Panel strongly recommends that adequate public support be provided for studies of the pathogenesis of pertussis and the biology of the organism, particularly as related to the immunology of pertussis, the complications of the disease, and the untoward reactions to immunization. Without such basic studies a more effective and safer pertussis vaccine cannot be developed.

2. Surveillance of pertussis in well-defined populations should be undertaken. Such surveillance would have three purposes: first, to determine the incidence of the disease in the United States, including distribution by age and vaccine status; second, to evaluate the possibility that a change in serotypes of *Bordetella pertussis* in a community causes outbreaks of pertussis in individuals previously immunized with serotypes formerly present; and, third, to determine whether the current infrequency of the disease in the United States may ultimately result in a population of older children and adults whose immunity has waned because of a lack of repeated exposure to the organism.

The Panel is convinced that currently employed surveillance systems to identify adverse reactions to pertussis vaccine are inadequate and recommends that definitive steps be taken by the appropriate subdivisions of the Public Health Service to improve them. Several alternatives are available. Perhaps the same channels as those proposed for reporting of adverse drug reactions can be utilized. Special field stations with sufficient populations under surveillance may have to be established and funded.

3. Specific recommendations of the Panel regarding the production, use, and evaluation of pertussis vaccines include the following:

The weight-gain test in mice used to determine toxicity of pertussis vaccine needs revision to include specifications regarding mouse strain(s) to be used as a reference standard. Studies should be undertaken to develop other assays predictive of human reactivity. Obviously, better definition of the organisms' biological characteristics (Recommendations, No. 1) would facilitate prediction and prevention of reactivity in man.

The agglutination test used to determine vaccine response in humans should be standardized. It is recommended that a reference serum be used for comparison. A reference laboratory should be available at the Bureau of Biologics. The interval between immunization and obtaining serum for testing of the serologic response must be specified. An acceptable titer obtained by a standardized method should be defined; titer rises or geometric means titers are not adequate to evaluate

immunogenicity. (See discussion on Efficacy, Pertussis Generic Statement.)

Regulations concerning the maximum human dose should be updated to reflect current recommendations and practices. It should be required that pertussis vaccine have a potency of 4 protective units per single human dose. The upper estimate of a single dose should not exceed 8 protective units.

The vaccine label should warn that if shock, encephalopathic symptoms, convulsions, or thrombocytopenia follow a vaccine injection, no additional injections with pertussis antigens should be given (immunizations can be continued with DT). The label should also include a cautionary statement about fever, excessive screaming, and somnolence.

Any fractionated vaccine that differs from the original whole cell vaccine should be field tested until better laboratory methods for evaluating immunogenicity in man are developed. Field testing should include agglutination testing and, if possible, evaluation of clinical efficacy in man.

4. Petussis vaccine is one of the immunizing agents for which it is strongly urged that legislation be enacted to provide reasonable Federal compensation to the few individuals injured and disabled by participating in a meritorious public health program. Such legislation would protect manufacturers and physicians against liability in situations in which the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccine.

Basis for Classification

Because field trials are not now feasible, at least in this country, the standard of efficacy upon which major reliance has to be placed is a mouse protection test, the results of which were correlated closely with the original field tests upon which evidence of efficacy for pertussis vaccine is based. Agglutination titers provide general but not absolute correlative support. Therefore, vaccines prepared in accordance with the specifications of those found effective in field trials and meeting standards for mouse protection are considered eligible for assignment to Category I especially when supported by adequate agglutination titers.

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SPECIFIC PRODUCT REVIEWS

Pertussis Vaccine Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* No data have been provided by the manufacturer for the monovalent pertussis vaccine, for which they are presently licensed.

2. *Labeling*—a. *Recommended use/indications.* No labeling was provided.

b. *Contraindications.* No labeling was provided.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

b. *Safety*—(1) *Animal.* No information was provided.

(2) *Human.* No information was provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be determined.

4. *Critique.* In the absence of any data from the manufacturer regarding the monovalent pertussis vaccine, and in the absence of any proposed labeling for this product, the Panel must necessarily recommend revocation of licensure for administrative reasons.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Pertussis Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* Pertussis vaccine adsorbed is a suspension of killed *Bordetella pertussis* organisms in 0.85 percent saline solution mixed with a suspension of aluminum phosphate (no more than 1.5 mg per single dose), and preserved with thimerosal, 0.01 percent. The number of organisms is equal to 8 to 16 opacity units per 0.5 mL. Formaldehyde is added "if needed" to a concentration of not more than 0.01 percent. Each 0.5 mL contains 4 protective units.

2. *Labeling*—a. *Recommended use/indications.* This product may be used alone for active immunization if it is desired to begin after 3 months or for booster during outbreaks. Routine